AIDS CONTROL USING STATE-DEPENDENT RICCATI EQUATION

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ABSTRACT: *: In this paper the state-dependent Riccati equation technique was used to control AIDS. First, the mathematical model of the variables was presented. Then, the effect of injecting drug on destroying the Human Immunodeficiency Virus, the healthy cells and the target cells was studied. Then the state-dependent Riccati equation was presented for an affine nonlinear system and finite horizon quadratic performance index. Finally the designed performance controller has been measured by defining various scenarios. The simulation results show that state-dependent Riccati equation meets the expected outcome.*

Keywords: State-dependent Riccati equation (SDRE), human immunodeficiency virus (HIV), Affine, Linear Quadratic Regulator (LQR), State Dependent Coefficient (SDC)

INTRODUCTION

AIDS is a rated disease that may destroy countries and disturb human communities in long-term. For this reason, the scientific community has focused on the development of mathematical models and definition of new strategies to control the proliferation and spread of AIDS to control the disease with useful and appropriate intervention methods [1 and 2]. The disease that caused the death of millions of people around the world is a serious problem for public health and therefore requires everyone's assistance in order to be controlled. Since the beginning of the disease the control methods through optimal control techniques have attracted a lot of attention which are discussed below.

The first detailed studies include modeling analysis associated with clinical results in 1999 show that the initial phase of the disease may be expressed by simple linear models. In [3] using a Taylor series approximation around the equilibrium point for a linear model, a state feedback controller is designed.

Despite the simplicity of this method, there are some drawbacks. For example, the resulting model is an approximate. The initial conditions must be close to equilibrium and in addition, achieving the sustainability is very difficult. Also if the linear system is uncontrollable the appropriate feedback design is not possible. Therefore in modeling AIDS it should be noted that this modeling is considered around the equilibrium point corresponding healthy people. If you follow this procedure, the linearization around the equilibrium point is performed corresponding to the severity of the disease. And the state feedback controller should guide the state of the system to the points away from equilibrium with the risk that the system is moving toward instability due to neglecting the higher-order terms. In some early researches the elimination of non-linearity in the system is realized using a static feedback.

In other examples of research papers the HIV treatment method is designed based on the control techniques including optimal control [4], adaptive control [5], nonlinear control based on Lyapunov methods and using disintegration in the form of feedback along with the step back method [6] and predictive control [7]. Also a variety of methods based on feedback control with time delay and Lyapunov function for the stability of a model for AIDS are presented [8]. In [9] an AIDS control strategy based on the nonlinear geometric control (fine line) is described without citing any adaptive control and considering a different model. A recent article in [10] described the application of the periodic control of drug delivery and its effects to control this disease. In [11] has designed the optimal controller for linear models in multi-drug AIDS (multiple entries) using the designed Yield for some of the state variables. [12] Has designed an optimal controller for an affine nonlinear system using SDRE technique and achieved relatively good results. In [13] the developed theories on nonlinear regulation are analyzed to so solve nonlinear optimal control problem, the solution, stability, and optimality properties associated with SDRE controller.

In [14, 15] the SDRE is introduced as the corrected version of the LQR to control nonlinear systems that have high convergence speed. In [16] for a class of nonlinear systems the form $\dot{x} = f(x) + g(x)u$ in which the Infinite horizon optimal regulation problem leads to solve the state-dependent Riccati equation. In [17] a model is presented to solve AIDS using SDRE optimized control in which the HIV drug is regulated.

2. Formulation of the problem

AIDS is a collection of diseases created in the body along with the weakness of the immune system by a virus called HIV. In other words, when HIV makes the body's immune system so weak that it becomes unable to fight off diseases that it used to inhibit them normally, then the human body has entered the stage of the disease describe briefly as the AIDS. The conventional methods of treatment of this disease include every day medication by the patient. These are mainly of two types of specific medicines and have severe side effects such as nausea and vomiting for consumers that in some cases lead to stop the treatment of many HIV-infected patients. The clinical experiments indicate the fact that there is a strong association between HIV status (number or size of the AIDS virus) and the immune system of the patient and existing treatment strategies. The scientists apply the mathematical models of AIDS growth based on the dynamic growth and development strategy for the treatment using the control methods. The mathematical model depends on the patient's immune system and the type of AIDS validated with experimental results. Then these models are incorporated into the proposed treatment strategy. Generally

the treatment effect is added to mathematical models of HIV as a control input. AIDS dynamics is based on a natural combination with mathematical models in the form of the nonlinear differential equation. As a result applying non-linear control strategy for such models will fail. On the other hand, linearization of nonlinear models will cause unwanted results. For example, it leads to uncontrolled spread of AIDS or toxic effects that may have a negative effect on the patient's life. Drug management in optimal AIDS treatment control is something described as minimizing the dose during treatment. In this method the managed amount of medication is considered as a control input to the system that makes a balance between normal cells, infected cells and the target cells. The purpose of control is to eradicate the infected population with the virus to minimize the injection. Various models are created and used to express the HIV infection in mathematical terms. These models are based on tests and reviews of changes in the infected individual over the time with the use of modeling and data obtained from the clinical data. In short we can say that when the HIV virus enters the individual's blood while proliferation a type of body immune cells (white blood cell material) in the blood called CD4 + Tcell prevent the proper production of the cell through involvement in copying RNA and in other words it infects the cell. The infected cell does not have a predetermined efficiency. In addition the infected cells start to produce HIV free virus and as this process continues the number of CD4 + Tcell is reduced per unit volume and the person in considered as infected with HIV cell. The equations of the AIDS model include:

$$\dot{T_1} = \lambda_1 - d_1 T_1 - (1-\epsilon) k_1 V_i T_1 \quad (1)$$

$$\dot{T_2} = \lambda_2 - d_2 T_2 - (1-f\epsilon) k_2 V_i T_2 \quad (2)$$

$$\dot{T_1^*} = (1-\epsilon) k_1 V_i T_1 - \sigma T_1^* - m_1 E T_1^* \quad (3)$$

$$\dot{T_2^*} = (1-f\epsilon) k_2 V_i T_2 - \sigma T_2^* - m_2 E T_2^* \quad (4)$$

$$\dot{V_i} = N_T \sigma (T_1^* + T_2^*) - [c + (1-\epsilon) p_1 k_1 T_1 + (1-f\epsilon) p_2 k_2 T_2] V_i \quad (5)$$

$$\dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{T_1^* + T_2^* + k_b} E - \frac{d_E (T_1^* + T_2^*)}{T_1^* + T_2^* + k_d} E + \sigma_E E \quad (6)$$

Where the normalized parameters and the independent variables are described below:

Table 1-The state variable of AIDS

Variable name	Description
T_1	Uninfected CD4 + target cells
T_2	Uninfected target cell type 2
T_1^*	Infected target cells
T_2^*	Infected target cells type 2
V_i	Infective viruses
E	Resistant effective

The control input ϵ is the drug concentration in the blood and the external drug injection that have two upper and lower bound constraints $0 \leq \epsilon \leq 0.75$. In the optimal treatment strategy the purpose is to minimize the amount of drug in the treatment. Based on the relations (1) to (6) state variables are as follows:

$$x = [x_1, x_2, x_3, x_4, x_5, x_6]^T = [T_1, T_2, T_1^*, T_2^*, V_i, E], u = \epsilon \quad (7)$$

$$\frac{dx_1}{dt} = \lambda_1 - (d_1 + k_1 x_5) x_1 - k_1 x_5 x_1 u \quad (8)$$

$$\frac{dx_2}{dt} = \lambda_2 - (d_2 + k_2 x_5) x_2 + f k_2 x_5 x_2 u \quad (9)$$

$$\frac{dx_3}{dt} = k_1 x_5 x_1 - \sigma x_3 - m_1 x_6 x_3 - k_1 x_5 x_1 u \quad (10)$$

$$\frac{dx_4}{dt} = k_2 x_5 x_2 - \sigma x_4 - m_2 x_6 x_4 - f k_2 x_5 x_2 u \quad (11)$$

$$\frac{dx_5}{dt} = N_T \sigma (x_3 + x_4) - [c + p_1 k_1 x_1 + p_2 k_2 x_2] x_5 + [p_1 k_1 x_1 + f p_2 k_2 x_2] x_5 u \quad (12)$$

$$\frac{Dx_6}{dt} = \lambda_E + \frac{b_E (x_3 + x_4)}{x_3 + x_4 + k_b} x_6 - \frac{d_E (x_3 + x_4)}{x_3 + x_4 + k_d} x_6 + \sigma_E x_6 \quad (13)$$

The parameters of the model have been defined and initialized as follows:

Description	The amount	Para meter
type 1 target cells production rate	10	λ_1
type 1 target cells disappearance rate	0.01	d_1
type 1 target cells infection rate	$8*10^{-4}$	k_1
clearance rate of the injected resistant type 1cells	0.01	m_1
type 1infective viruses average number	1	p_1
Infected cells elimination rate	0.7	σ
reduced effectiveness of the drugs in type 2 population	0.34	f
Resistant effectives' production rate	$1*10^{-3}$	λ_E
The maximum production rate of resistant effectives	0.3	b_E
Saturation constant of the production resistant effectives	0.1	k_b
type 2 target cells production rate	$31.98*10^{-3}$	λ_2
type 2 target cells disappearance rate	0.01	d_2
type 2 target cells infection rate	0.1	k_2
clearance rate of the injected resistant type 2cells	0.01	m_2
type 2infective viruses average number	1	p_2
Rate of natural loss of viruses	13	c
The ratio of the produced virions to the infected cells	100	N_T

The natural rate of loss of resistant effectives	0.1	σ_E
The maximum rate of loss of resistant effectives	0.25	d_E
Saturation constant of the production resistant effectives	0.5	k_d

In the practical cases a person with AIDS may suffer from fluctuations caused by sudden changes in viral cells, thermal changes, Time-varying parameters change during treatment caused by the environmental changes [18]. In this situation access to the desired response may be affected. If the changes in the parameters are neglected the optimal treatment will not be resistant enough so there is a need for an optimal method of control [19]. In this study the optimal controller of the nonlinear AIDS is designed using the state-dependent Riccati equation and by simulating various scenarios specially the change of model parameters the designed controller performance is evaluated. Recent advances in the use of mathematical modeling in the field of medical science have created an incentive to use mathematical models for more accurate in study of AIDS. The models used analyze the behavior of the immune system, the effects of infection on the system and the performance of these systems and their effects on the disease. Using this model it is possible to simulate the treatment strategies aimed at reducing infected cells. Also various control issues can be implemented and evaluate the disease process over time.

Furthermore, in the system of linear optimal control as a linear function, the time-varying state variables are obtained by the state variables and solving the Riccati equation. But in nonlinear systems obtaining optimal control rule is not possible by solving their Riccati equation. Various optimal control methods are proposed for these systems and the state-dependent Riccati equation is one of the most efficient methods.

3. The nonlinear optimal controller design:

Linear quadratic regulation (LQR) is a rational and cost effective method to optimize the linear systems. But most control systems and operational processes are nonlinear. The modified LQR version is specific to nonlinear systems, Riccati equations (SDRE[1]) that has a high convergence speed. This method is a controller design based on nonlinear feedback that extracts the optimal response of the system and pursues the appropriate path. Consider the following nonlinear affine system:

$$\dot{x} = f(x) + g(x)u \tag{14}$$
$$y = h(x)$$

Where $x \in R^n$ is the state variables system's vector $u \in R^m$ is the input vector , $y \in R^p$ is the output vector and f(x) and g(x) are in general nonlinear function. Now if it is possible to write the nonlinear system as state-dependent coefficient (SDC), i.e. if we write the vector f (x) as f (x) = A (x) x and g(x)= B(x) with the state matrix A (x) and B(x), we have:

$$\dot{x} = A(x)x + B(x)u \tag{15}$$

In this case assuming that all state variables are available for feedback the aim of using SDRE controller is to find control law with gain feedback k(x) as $u = -k(x)x$ such that the finite horizon quadratic performance index is minimized:

$$J(x,u) = \int_{t_0}^{t_f} (x^T Q(x)x + u^T R(x)u)dt \tag{16}$$

Where Q(x) is positive semi-definite symmetric matrix, $x^T Q(x)x$ is the degree of control accuracy, R(x), symmetric positive definite matrix, $u^T R(x)u$ is a value for control effort. In fact SDRE controller can establish a balance between effort and precision control system. By solving Hamilton equations u (x) can be chosen as follows:

$$u(x) = -R(x)^{-1}B(x)^T P(x)x \tag{17}$$

Where P (x) is a single symmetric and positive matrix and the solution of the SDRE equation is:

$$\dot{P}(x) + P(x)A(x) + A^T(x)P(x) - P(x)B(x)R(x)^{-1}B^T(x)P(x) + Q(x) = 0 \tag{18}$$

Although the A (x) and B (x) d Matrix are optional but they should be chosen so that the closed loop system is stable and is at least manageable. In this paper, the matrix B(x) and A(x) are as follows.

$$A(x) = \begin{bmatrix} -d_1 & 0 & 0 & 0 & -k_1x_1 & 0 \\ 0 & -d_2 & 0 & 0 & -k_1x_2 & 0 \\ k_1x_5 & 0 & -\sigma - m_1x_6 & 0 & 0 & 0 \\ 0 & k_2x_5 & 0 & -\sigma - m_1x_6 & 0 & 0 \\ -p_1k_1x_3 & -p_2k_2x_3 & N_T\sigma & N_T\sigma & -c & 0 \\ 0 & 0 & a_{63} & a_{64} & 0 & \sigma_E \end{bmatrix}$$

(19

$$a_{63} = a_{64} = \frac{b_E x_6}{x_3 + x_4 + k_b} - \frac{d_E x_6}{x_3 + x_4 + k_d}$$

$$B(x) = \begin{bmatrix} -k_1x_5x_1 \\ fk_2x_5x_2 \\ -k_1x_5x_1 \\ -fk_2x_5x_2 \\ [p_1k_1x_1 + fp_2k_2x_2]x_5 \\ 0 \end{bmatrix} \tag{20}$$

4. SIMULATION RESULTS

By defining a number of different scenarios the function of SDRE controller is studied. In Figures 1 and 2 the response of the uncontrolled system (without medication) have been investigated. The axis of horizontal is based on time and the axis of vertical is the state variables for different initial conditions.

[1] *State Dependent Riccati Equation*

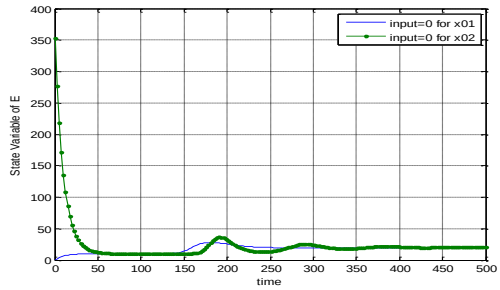

Figure 1- the changes of resistant effectives for different initial conditions

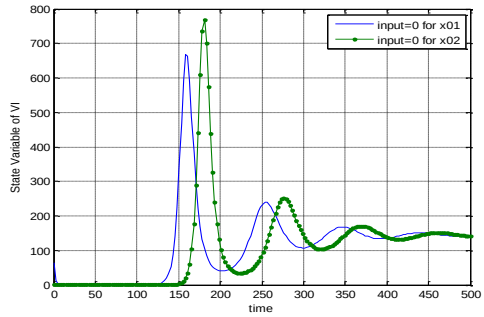

Figure 2 – changes for infected viruses for different initial conditions

In the above figures it can be seen that without medication the viruses grow fast and minimize the resistant cells.

Situation 1:

In this situation, under basic conditions $T_1(0) = 163, T_2(0) = 0.005, T_1^*(0) = 12, T_2^*(0) = 0.05, V_i(0) = 64,$ analyzes the system response by applying weight matrix in various cases $r = 10^7, q = \begin{bmatrix} 500 & 0 \\ 0 & 500 \end{bmatrix}$ and $r = 5 * 10^7, q = \begin{bmatrix} 1000 & 0 \\ 0 & 1000 \end{bmatrix}$

$$J = \int_0^{500} (q_{11}(x_5 - 0.4)^2 + q_{22}(x_6 - 353)^2 + ru^2(t))dt \quad (21)$$

Figures (3) to (5), show the control optimal solution by SDRE method.

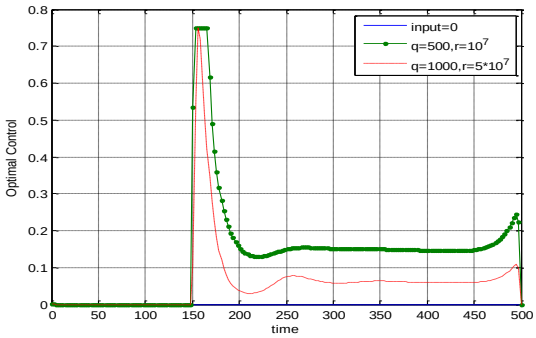

Figure 3 - optimized input Changes for different amounts of weight control

It can be seen that with reduced r weight the input range is narrow and for reduced input r the input range is wide.

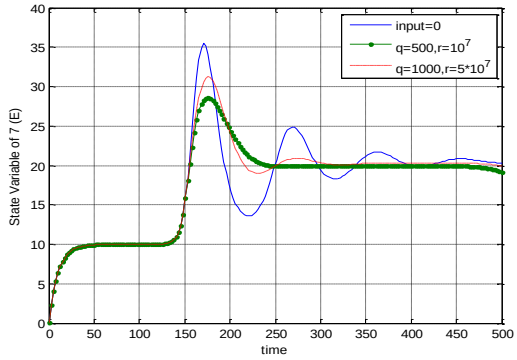

Figure 4 - Changes of resistant effectives to the different control weights

As you can see, if the drug input is not applied the number of resistant effective cells have many changes. While if the drug input is applied the number of resistant effective cells converge to a constant value.

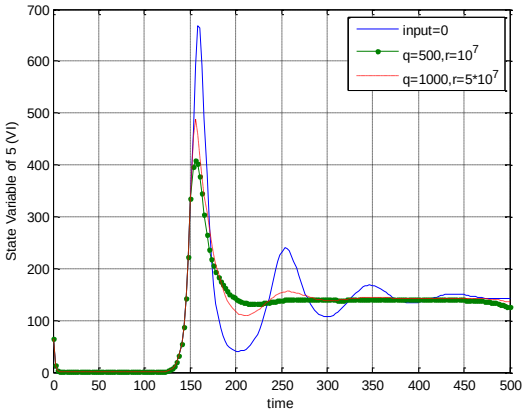

Figure 5 - Changes in infective viruses for different weight control

In the image above you can see that without applying the input the changes of infective viruses was high. While for optimized input and appropriate weight control the number of infective viruses is considerably reduced.

Situation 2:

In this situation, under basic conditions $T_1(0) = 968, T_2(0) = 0.6, T_1^*(0) = 0.08, T_2^*(0) = 0.006, V_i(0) = 0.4, E(0) = 353$ analyzes the system response by applying weight matrix in various cases $r = 10^7, q = \begin{bmatrix} 500 & 0 \\ 0 & 500 \end{bmatrix}$ and $r = 5 * 10^7, q = \begin{bmatrix} 1000 & 0 \\ 0 & 1000 \end{bmatrix}$. Figures (3) to (5), show the optimal control solution in this condition.

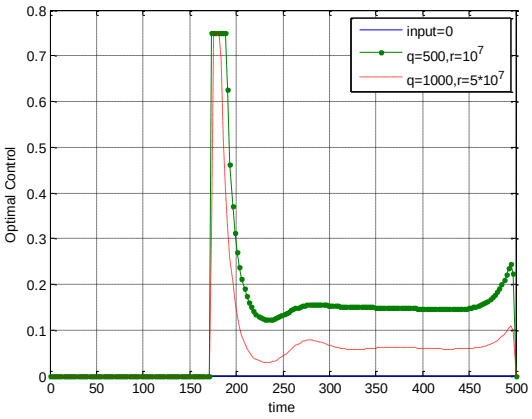

Figure 6 – Changes of optimized inputs for different amounts of weight control

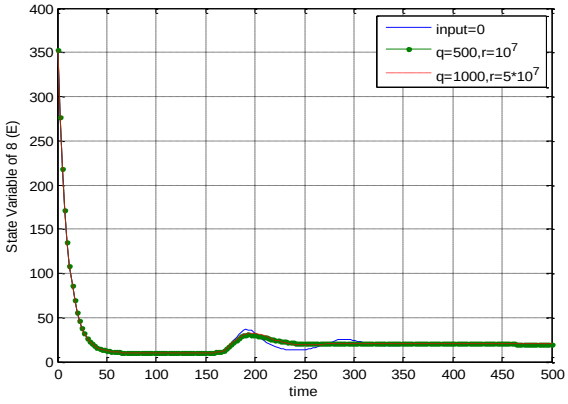

Figure 7 - Changes of resistant effectives to the different control weights

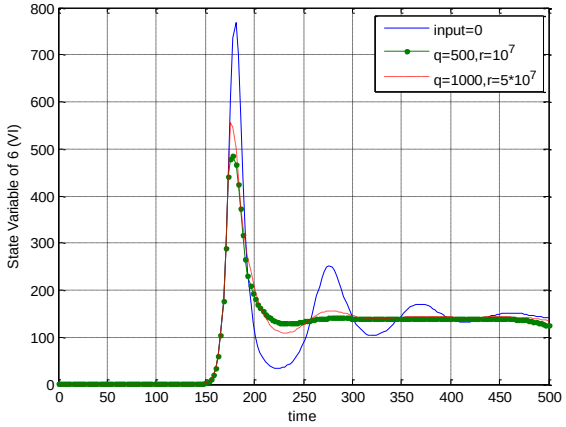

Figure 8 - Changes in infective viruses for different weight control

As you can see above in Figures the behavior of the variables is similar to situation 1.

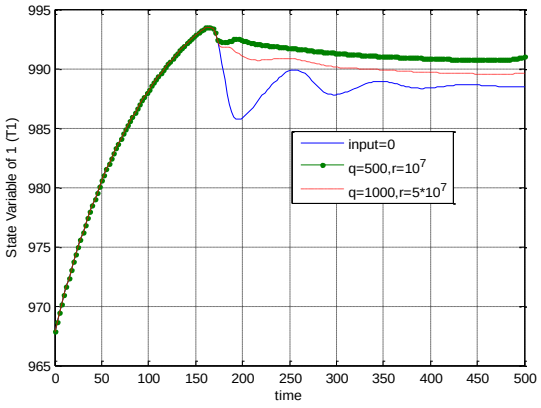

Figure 9 - uninfected CD4 + target cells

In this figure you can observe that by applying the inputs the rate of the uninfected cells is increased.

5. CONCLUSION:

In recent years, various controllers have been used for the proper administration of medications and faster recovery for patients with AIDS. But in these controllers the changes of model parameters over time for the patient is less considered. In this paper, using the SDRE the optimal controller for a nonlinear model of HIV in the body is designed. Simulation results show that this method provides a fast and easy treatment management. The SDRE performance depends on the choice of state-dependent weighted matrices. The results show that the optimal SDRE control can be used effectively to manage medication in future.

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1 SDRE (State Dependent Riccati Equation)
2 HIV (human immunodeficiency virus)
3 Affine
4 LQR (Linear Quadratic Regulator)
5 SDC (State Dependent Coefficient)
6 Linear Quadratic Regulation
7 State Dependent Riccati Equation
8 State Dependent Coefficient